

Appl. No. : 09/905,088
Filed: : July 12, 2001

45. (Once amended) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245).

c7 46. (Once amended) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide.

c8 49. (Once amended) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393.

Remarks/Arguments

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, claims 39-51 were pending in this application and were rejected on various grounds. Claims 47 and 48 have been cancelled. The rejection of the remaining claims is respectfully traversed.

Oath/Declaration

1) The Examiner alleges that the oath or declaration is defective due to non-initialed and/or non-dated alterations and since it does not identify the citizenship of each inventor.

Applicants submit that a supplemental Application Data Sheet for the above identified application was sent on December 19, 2002 to the USPTO. Hence, Applicants submit that this objection is moot and herewith, provide a copy of the Application data sheet for the Examiner's convenience.

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Specification

2-4) The specification has been objected to for containing embedded hyperlink and/or other form of browser-executable code. The foregoing amendment, which deleted all embedded hyperlinks, is believed to overcome this objection.

The title was objected to as being non-descriptive. The foregoing amendment, which replaces the original title with a new, descriptive title is believed to overcome this objection.

Claim Objection

5) Claims 45-49 are objected to because of a missing "." after the recitation of the claim number. Claims 47 and 48 are canceled and hence the rejection to these claims are moot. In the remaining claims, the foregoing amendment which amends the claim numbers to incorporate the missing period is believed to overcome the objection.

Claim Rejections – 35 USC §101 and § 112

6) Claims 39-51 are rejected as allegedly not being supported by either a credible, specific and substantial asserted utility, or a well established utility. According to the rejection, the specification "does not teach any significance or functional characteristics of the polypeptide (SEQ ID NO: 245). The specification also does not disclose any specific methods or working examples in which the polynucleotides and polypeptide of the invention are shown to be involved in any activity."

Applicants disagree, and respectfully traverse the rejection.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

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The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a “substantial” utility.” (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P., 2107 II (B) (1) gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, the Utility Guidelines restate the Patent Office’s long established position that any asserted utility has to be “credible.” “Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant’s assertions.” (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Proper Application of the Legal Standard

Applicants submit that the polypeptides claimed in the present application have a specific, substantial and credible asserted utility, which are sufficiently described in the specification.

Applicants rely on the PDB12 cell inhibition data (page 207, lines 2-18) in support of patentable utility. These data were first disclosed in PCT/US98/19330 on September 16, 1998, the priority of which is claimed in the present application.

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Example 70 describes a cell-based assay, in which the PRO 293 polypeptide has been demonstrated to have the ability inhibit protein production by PDB12 pancreatic ductal cells, using an AlamarBlue™-based cell proliferation assay.

Cell culture models are a valuable tool for life science researchers, since they permit the study of a single cell type, and, through determination of cell proliferation and viability, enable researchers to assess the efficacy of potential therapeutic agents in the prevention and treatment of disease processes associated with the particular cell type studied.

AlamarBlue™-based assays in particular have been widely used in the study of cell proliferation and cell viability. The internal environment of the proliferating cell is more reduced than that of a non-proliferating cell, and the ratios of NADPH/NADP, FADH/FAD, FMNH/FMN, and NADH/NAD increase during cell proliferation. AlamarBlue™ can be reduced by such metabolic intermediates, the reduction is accompanied by a measurable shift in color, which, in turn, can be monitored by measuring absorbance spectrophotometrically, or by measuring fluorescence. The assay described in Example 70 of the present application uses fluorescence read-out, which allows one to calculate total cellular protein concentration produced by PDB12 pancreatic ductal cells in the presence and absence of a particular test molecule, such as PRO 293 polypeptides or chimeric PRO 293 polypeptides. Accordingly, the results of this assay can be considered as a secondary read-out for cell number, and are suitable for the assessment of the biological effect of a test substance on pancreatic cells. The data presented in Example 70 clearly demonstrate that the PRO 293 polypeptide inhibits protein production by PDB12 pancreatic cells. Accordingly, such PRO293 and PRO293-like polypeptides are useful drug candidates in the treatment of pancreatic disorders wherein such inhibition is desirable, such as pancreatitis, e.g. chronic alcoholic pancreatitis, which is known to be accompanied by ethanol-induced protein secretory alterations, and increased intraductal protein precipitation.

As set forth in M.P.E.P, 2107 II (B) (1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. The logic underlying the asserted utility in the present case is not inconsistent with general knowledge in the art, and would be considered credible by a person skilled in the art. It is, of course, always possible that an invention fails on its way of development to a commercial

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product. Thus, despite recent advances in rational drug design, a large percentage of drug candidates fails, and never makes it into a drug product. However, the USPTO is not the FDA, the law does not require that a product (drug or diagnostic) be currently available to the public in order to satisfy the utility requirement.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

7) Claims 39-51 are rejected under 35 U.S.C. 112, first paragraph for alleged lack of enablement. According to the rejection, "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In response to the previous rejection, Applicants have shown that the claimed polypeptides have a specific and substantial asserted utility, hence the present rejection should be withdrawn.

8-9) Claims 39-43 and 50-51 are rejected since: the specification does not teach variant PRO293 polypeptides nor discloses methods or working examples for "naturally occurring allelic variant" or "variants from a different species"; for lack of enablement for functional or structural characteristics of the fragments recited in the claims; and, for lack of reasonably conveying to the skilled artisan the possession of the claimed invention by the inventor at the time the application was filed. Applicants have construed that the underlying reason for the Examiner's lack of enablement rejection is the broad scope of the claims and the absence of any functional limitations in the claims.

Applicants submit that the claims have been amended to recite a functional limitation, namely, "polypeptides capable of inhibiting protein production in a cultured cell assay." Applicants rely on the PDB12 cell inhibition data (page 207, lines 2-18) in support of such enablement, which has been discussed in detail above. Procedures to identify and isolate variant proteins of SEQ ID 245 that show equivalent results in assays like the PDB12 cell inhibition assay were well known at the effective filing date of the present application. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-charge cell Culture*

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Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff. sub nom.*, *Massachusetts Institute of Technology v A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. cir. 1985) M.P.E.P. 2164.01. Indeed, the *in vitro* data provided in the cited example and the specification in general, coupled with the general knowledge in the art at the time of filing of the invention, provides sufficient guidance to the skilled artisan to make and use this invention without undue experimentation.

Thus, the claimed polypeptides have been fully enabled and sufficiently described in the specification of the present application.

10) Claims 39-43 and 50-51 are rejected as being "indefinite," since, PRO293 is a soluble protein which is not disclosed as being expressed on a cell surface. Thus, the extracellular domain (recited in claim 39) was not clear since art-recognized soluble proteins do not have such domains. The current claim amendments, which remove all references to the extracellular domain, are believed to overcome this rejection. Accordingly, the present rejection is believed to be moot, and should be withdrawn.

Attached hereto is a marked-up version of the amendments made to the specification and claims, entitled "**Version with markings to show changes made.**"

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No: 39780-1618P2C31). Please direct any calls in connection with this application to the undersigned at the number provided below.

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Respectfully submitted,

Dated: March 3, 2003

By: 

Ginger R. Dreger
Registration No. 33,055
Attorney of Record

HELLER ERHMAN WHITE & McAULIFFE LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, CA 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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Version with markings to show changes made

In the Specification:

The original title has been canceled, and replaced with the following new title: ---- Anti-PRO293 polypeptide.--

The paragraph, beginning at page 69, line 6, has been amended as follows:

--Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). [The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov>.] NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph, beginning at page 71, line 26, has been amended as follows:

--Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). [The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov>.] NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph beginning at page 147, line 27, has been amended as follows:

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (e.g., Dayhoff, GenBank), and proprietary databases (e.g. LIFESEQTM, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul, and Gish, Methods in

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Enzymology 266: 460-80 (1996)[; <http://blast.wustl.edu/blast/README.html>]) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a Blast score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

The paragraph, beginning at page 154, line 14 has been amended as follows:

--The EST sequence accession number AF007268, a murine fibroblast growth factor (FGF-15) was used to search various public EST databases (e.g., GenBank, Dayhoff, etc.) The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)[; <http://blast.wustl.edu/blast/README.html>]] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. The search resulted in a hit with GenBank EST AA220994, which has been identified as stratagene NT2 neuronal precursor 937230.--

The paragraph beginning at page 167, line 30, has been amended as follows:

--The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQTM, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington[; <http://bozeman.mbt.washington.edu/phrap.docs/phrap.html>]).

The paragraph beginning at page 178, line 14, has been amended as follows:

--The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used

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to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington[; <http://bozeman.mbt.washington.edu/phrap.docs/phrap.html>]).--

In the Claims:

Please amend Claims 39-44 as follows:

39. (Once amended) An isolated polypeptide having at least 80% amino acid sequence identity to:
- (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245);
 - (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide; or,
 - (c) [the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO:245);
 - (d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide; or
 - (e)] the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393, wherein the polypeptide is capable of inhibiting protein production in a cultured cell assay.
40. (Once amended) The isolated polypeptide of Claim 39 having at least 85% amino acid sequence identity to:
- (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245);
 - (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide;

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- (c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO:245);
- (d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide; or
- (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393, wherein the polypeptide is capable of inhibiting protein production in a cultured cell assay.

41. (Once amended) The isolated polypeptide of Claim 39 having at least 90% amino acid sequence identity to:

- (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245);
- (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide;
- (c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO:245);
- (d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide; or
- (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393, wherein the polypeptide is capable of inhibiting protein production in a cultured cell assay.

42. (Once amended) The isolated polypeptide of Claim 39 having at least 95% amino acid sequence identity to:

- (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245);
- (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide;
- (c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO:245);
- (d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 96 (SEQ ID NO:245), lacking its associated signal peptide; or

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- (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393, wherein the polypeptide is capable of inhibiting protein production in a cultured cell assay.
43. (Once amended) The isolated polypeptide of Claim 39 having at least 99% amino acid sequence identity to:
- (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245);
 - (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide;
 - (c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO:245);
 - (d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide; or
 - (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393, wherein the polypeptide is capable of inhibiting protein production in a cultured cell assay.
44. (Once amended) An isolated polypeptide comprising:
- (a) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245);
 - (b) the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO: 245), lacking its associated signal peptide;
 - (c) [the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO: 245);
 - (d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 86 (SEQ ID NO: 245), lacking its associated signal peptide; or
 - (e)] the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393, wherein the polypeptide is capable of inhibiting protein production in a cultured cell assay.
45. (Once amended) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245).

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46. (Once amended) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide shown in Figure 86 (SEQ ID NO:245), lacking its associated signal peptide.
47. Cancel.
48. Cancel.
49. (Once amended) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209393.
50. A chimeric polypeptide comprising a polypeptide according to Claim 39 fused to a heterologous polypeptide.
51. The chimeric polypeptide of Claim 50, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.